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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,936	01/14/2004	Douglas D. Burkett	344-P-32-USA	6529

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,936	BURKETT, DOUGLAS D.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed is acknowledged and has been entered. Claim 1 has been amended. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The substitute specification comprising the amendments as suggested by the Examiner in the previous Office action is acknowledged. However the substitute specification could not be entered because an accompanying clean version (without markings) and a statement that the substitute specification contains no new matter was not provided. Applicant must supply a clean version of the specification without any marking and a statement that the substitute specification contains no new matter (See 37 CFR 1.1.25 or MPEP 601.01(q)).

Previous Rejection

4. The claim rejection under 35 USC 112 first paragraph is withdrawn in view of Applicant's amendment. The claim rejection under 35 USC 112 second paragraph is withdrawn. The prior art rejection under 35 USC 103 is maintained and discussed below.

Claim Rejections - 35 USC § 103

Issue: The claim 1 is rejected under 35 USC 103(a) as being unpatentable over Mashberg et al in view of Rosin et al.

Applicant's traversal:

5. Applicant traverses the rejections on the following grounds: Applicant states that the prior art problem of the Mashberg-type staining protocol was that it was perceived (even by Mashberg himself) as having high rate of "false-positives". Applicant states that in fact, Mashberg's US 4,321,251 patent was specifically directed to reducing the number of false positives. Applicant contends that that problem persist, as indicated by US patent 5,372,801 to Tucci et al., which sough to avoid the complexity of the procedure of Mashberg '251 for reducing false positive. Applicant states that there was not even a consensus as to the reason for "false positives" or the mechanism of staining. Applicant states that for example, the US Patent 5,882,627 reported that the selective staining was due to the ability of the dye to penetrate normally tight intracellular junctions in cancerous tissue, while Tucci '801 attributed "false positives" to "non-specific staining" of mucosal tissue and, finally, the true mechanism of selective dye staining was disclosed as mitochondrial staining in US patent 6,649,144. Applicant states that none of the prior workers had any idea that the vast proportion or reported "false positives" were not in fact false.

Applicant asserts that the prior art problem with the genetic alteration analysis protocol was that one had to wait until there was visual indication, e.g., a lesion, to know where to take a tissue sample for genetic analysis, i.e., after the tissue had already progressed to cancer. Applicant states that alternatively, analysis of body fluids would detect possible cancer or precancer, but again one could not tell where to tale a tissue sample for genetic analysis or regular histological examination. Applicant states that however, by combining these two protocols, one obtains immediate direction as to where to take the tissue sample and an

immediate forecast (prognosis) that cancer may develop, even before; there is any visual indication of it. Applicant states that a full 80% of the samples identified by selective dye staining are "clonal" - including those previously thought to be "false positives"- and are therefore, in the progression pathway to cancer and 50-75% o these samples will progress to invasive cancer.

Applicant states that these protocols (and their respective disadvantages and problems) had existed side-by-side in the art for years, until Applicant made the connection here disclosed and asserted in amended claim 1. Applicant concludes that by the claimed method, genetic molecular analysis, with its huge advantages over conventional histology --prognosis versus after the fact diagnosis -- can now become mainstream. Applicant states that the objective evidence clearly rebuts the prima facie case of obviousness proposed by the Examiner.

Examiner's Response:

6. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments, MPEP 2143 states

"[T]o establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In this case, the cited prior art meets the requirements to establish a *prima facie* case of obviousness. First, the combination of Mashberg in view of Rosin provides motivation for establishing obviousness. The primary reference of Mashberg teach all limitations of the claims except extracting DNA from the resected tissues and examining the DNA for allelic losses for

mutations of tumor suppressor genes. Mashberg provides motivation for subsequent analysis in the teaching that "a negative biopsy should not be accepted as the final word if a tissue sample is considered suspicious for malignancy" (see page 349, col. second full paragraph). Mashberg suggests further analysis and/or biopsy be performed on the suspected sampled. The secondary reference of Rosin provides the limitations not found in the Mashberg reference and provides motivation for performing further analysis on biopsy tissue samples. Rosin teach that the method, wherein DNA extracted from biopsy tissue is analyzed for allelic loss or tumor suppressor genes, is a more sensitive technique for studying clonal changes in tumor and premalignant lesion. Secondly, the combination of Mashberg and Rosin provides a reasonable expectation of success in the teaching by Rosin et al that the analysis procedure disclosed therein is advantageous because it only requires small quantities of DNA, yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes. The primary reference of Mashberg supports these additional analysis and consultation (see page 347-349). The secondary reference of Rosin further teaches that information critical to genetic events can be obtained using the analysis method even before the identification of the actual suppressor. This teaching by Rosin suggest early prognosis of cancer. Finally, as noted above, the combination of Mashberg and Rosin provides all of the limitations of the claims as rejected and currently amended.

In response to Applicant's arguments concerning the prior art problem with the Mashberg-type staining protocol, it is noted that the US patents argued by Applicant were not recited in the rejected claims, rather the Examiner relied on a review article written by Mashberg (see prior office action for citation). Nonetheless, while it is noted that Mashberg teaches at page

347, col. 2 " that "[T]he great value of toluidine blue staining lines in its control over "false-negative clinical finding", it appears that Applicant applies the staining dye for the same purpose as Mashberg because the claim recites in step 1 that "a staining dye is applied to the tissue having the DNA such that the dye is *selectively retained* by mitochondria of neoplastic and preneoplastic cells". Thus, contrary to Applicant's arguments, it appears that Applicant also waits for a visual indication to know where to resect the tissue sample for further analysis. Therefore, an immediate diagnosis as Applicant argues is not readily apparent in the claims as currently written. Applicant's arguments are not sufficient to overcome the prior art rejections. Accordingly, the rejection under 35 USC 103 is maintained.

New Ground of Rejection

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANTS AMENDMENT TO THE CLAIMS:

Claim Rejections - 35 USC § 112: New Matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to the claim to recite "epithelial cancer" was not found anywhere in the

specification as filed. The specification teaches in the Examples that the method relates to head and neck cancer (page 16). While the specification teaches the use of epithelial tissue in the staining analysis method, the specification makes no reference to any epithelial cancer, which broadly encompasses numerous cancer types (e.g., breast, prostate, colon, and etc) that are not adequately described or disclosed. Thus, the specification does provide support for the invention as currently claimed.

Conclusion

9. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail.

Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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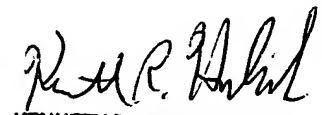

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
7/6/06